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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,868	06/04/2002	Hans Deckmyn	50304/064001	2345

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/049,868	DECKMYN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65,66,70,71,80-82,84 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *80-82,84 and 85* is/are allowed.

6)☒ Claim(s) *65 and 66* is/are rejected.

7)☒ Claim(s) *70 and 71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/13/07, is acknowledged.

2. Claims 65-66, 70-71, 80-82 and 84-85 are pending and under examination in the instant application.

3. Applicant's IDS, filed 3/13/07, is acknowleged.

4. In view of the amendment filed on 3/13/07, only the following rejections are remained.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 65-66 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising the monovalent antibody fragment obtained from the monoclonal anti body produced by the cell line deposited with LMBP 5108CB or the variable region of a monovalent antibody fragment comprises SEQ ID NO: 4 and a pharmaceutical acceptable carrier, does not reasonably provide **enablement** for a pharmaceutical composition comprising any monovalent antibody fragment with binds in vivo to human platelet glycoprotein GPIb without incurring thrombocytopenia in claim 65, wherein the fragmen is a Fab fragment or a single variable domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 9/13/06.

Applicant's arguments, filed 3/13/07, have been fully considered, but have not been found convincing.

Applicant points to Example 6 of Applicants' specification describes how to assess inhibition of vWF binding using standard methods known in the art at the time the application was filed. Example 6 extensively illustrates how to perform ristocetin-and botrocetin-induced aggregation assays to study whether vWF interacts with GPIb. In this regard, Applicants again direct the Examiner's attention to the Declaration of Dr. Hans Deckmyn previously filed in this case. Dr. Deckmyn, using standard methods known at the time the application was filed, generated Fab fragment of RMP 15 (Kulkarni et al., Journal Clinical Investigation 105:783-791, 2000). Dr. Deckmyn further provided data on the anti-GPIb alpha antibody RPM15. Dr. Deckmyn also noted that, even though RPM 15 induces thrombocytopenia as IgG, the monovalent RMP 15 Fab fragments do not induce thrombocytopenia in vivo.

However, the Examiner notes that the previous Office Action states that the specification is enabled for a pharmaceutical composition comprising the monovalent antibody fragment obtained from the monoclonal anti body produced by the cell line deposited with LMBP 5108CB.

Regarding Bergmeier believed that thrombocytopenia results from the binding between the antibody and its GPIb epitope. Applicants in fact have proved Bergmeier to be incorrect. See, for example, Applicants' specification at page 8 (lines 19-23). Thus, Applicants submit that this line of reasoning does not support the asserted lack of enablement of the presently claimed invention.

However, the totality of what is publicly known at the time the invention was made is considered. Further, the specification on page 18, lines 19-23, refers to 6B4 mAb, which the previous Office Action stated was enabled.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 65-66 stand rejected under 35 U.S.C. 102(b) as being anticipated by Tandon et al (Biochem. J. (1991) 274:435-542) for the same reasons set forth in the previous Office Action mailed 9/13/06.

9. Claims 65-66 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wicki et al (Eur J Biochem. 1985 Nov 15;153(1):1-11) for the same reasons set forth in the previous Office Action mailed 9/13/06.

Applicant's arguments, filed 3/13/07, have been fully considered, but have not been found convincing.

Applicant argues that both Tandon and Wicki fail to teach a "pharmaceutical composition" as claimed because these references fail to teach not only a composition that includes a concentration of an antibody sufficient to bring about a therapeutic effect, but also fail to teach compositions that are pharmaceutical compositions which would be introduced into an appropriate subject. Applicants direct the Examiner's attention to the Declaration of Dr. Desire Collen under 37 C.F.R 1.132 to

However, the Declaration of Dr. Desire Collen filed on 3/13/07 under 37 CFR 1 .132 has been considered but is ineffective to overcome the Tandon et al and Wicki et al rejections under 102(b) of record.

The declaration of Dr. Collen (¶7) states that Tandon and Wicki described the use of the anti-GP1b Fabs in vitro, i.e. on isolated platelets or blood samples. The Tandon and Wicki compositions are not pharmaceutical compositions because each lacks the sterility which is

inherently required for every pharmaceutical composition; in particular, compositions that include an antibody. Moreover, because Tandon and Wicki were investigating the role of GPIb in platelet function in vitro, the compositions used by Tandon and Wicki do not require that they are sterile. Tandon and Wicki therefore do not describe pharmaceutical compositions as presently claimed in this application.

However, it is a common practice in the laboratories to sterile filter the buffers. Further, declaration only speculates that the buffers used in both references are non-sterile.

The declaration on (¶ 8) states that Tandon and Wicki compositions described in the context of in vitro experiments as pharmaceutical compositions is the fact that the Tandon and Wicki compositions are neither selected in view of tolerance by the patient nor based on the desired activity of the GPIb antibody fragment. Indeed, antibody fragments are generally provided in pharmaceutical compositions either freeze-dried or in saline, or in another physiologically neutral solution. The inclusion of buffers typically used in *in vitro* experiments renders such compositions unsuitable as pharmaceutical compositions.

However, the buffers used in the prior art would appear to be compatible with physiological conditions, and not incompatible with pharmaceutical use. Since the specification discloses that that typical carriers include biocompatible aqueous buffers (see ¶6 of the Dec.) the prior art's taught by both Tandon and Wicki would appear to be encompassed by the broadest reasonable definition of a "pharmaceutical carrier".

The declaration, on ¶ 9, states that 9. that Tandon et al describe the use of a Buffer A. Buffer A includes 50mM Tns and 0.5%8SA. Tris (or Trishydroxymethylaminomethane) is an irritating product and is generally used for its strong buffering capacity, which can be relevant when working with different reagents in small volumes. Tris will however not be included in a pharmaceutical composition comprising antibody fragments, in view of its toxicity and the fact that antibodies either in the composition or upon administration to the patient remain under physiological conditions, such that there is no need for a strong buffering reagent. BSA (bovine serum albumin) is generally used in *in vitro* assays to avoid non-specific protein interaction. Platelets isolated from their natural environment (blood) are contacted with a BSA-containing buffer to avoid non-specific interaction of any peptide or protein with the platelets. There is however no reason to include BSA in a pharmaceutical composition that includes antibody fragments. Indeed, upon administration of the antibodies, the numerous proteins present in the body (including albumin) will ensure that non-specific interactions are avoided. Furthermore, in view of the very strict regulation on the very strict regulation on the inclusion of bovine products in pharmaceutical compositions, the presence of bovine serum albumin in a composition comprising antibody fragments would make it unsuitable as a pharmaceutical composition.

However, many pharmaceutical compositions elicit toxic side effects, nonetheless, they are still pharmaceuticals. Also, the reference teachings anticipate the claimed invention because the specification provides no guidance regarding toxicity level of the pharmaceutical composition.

In addition, many references uses Tris buffer as pharmaceutically suitable diluents. Applicant attention is directed to for example, US. Pat. 6,998,469 , col., 30, lines 33-51.
Further, the Examiner calls Applicant's attention to US. Pat. 5,958,765 which teaches that formulation of antibodies in pharmaceutically acceptable form may be effected by known methods, using known pharmaceutical carriers and excipients. Suitable carriers and excipients include but by way of example buffered saline, Bovine serum albumin, ect (see col., 20, lines 50-55).

The declaration on ¶10 states that the Tandon and Wicki compositions also do not contain a sufficient amount of monovalent antibody to bring about a therapeutic effect, and therefore the compositions are not pharmaceutical compositions.

However, the claims do not cite limitation on sufficient amount in the claimed composition. That is Applicant argues limitation not claimed.

In the remarks Applicant argues that no evidence is provided demonstrating that one would understand that an antibody in such an elution buffer would be useful as a pharmaceutical composition. In addition, apart from the sterility issue discussed above, Applicants note that it is common practice to add sodium azide, as an antimicrobial agent, to gel filtration buffers at a concentration around 0.02%. For this reason too, given the toxicity of sodium azide, the Ultrogel AcA-34 elution buffer cannot be considered a pharmaceutical composition.

However, there is no evidence that the elution buffer contain sodium azide. Also, the specification discloses that suitable pharmaceutical carriers may include antibacterial and antifungal agents.

10. Claims 80-82 and 84-85 are allowed.

11. Claims 70-71 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. The following reference are provided as art of interest:

A. US. Pat. No. 7,112, 661 teaches and claims human scFv GPIb antibodies and a composition thereof.

B. Miller JL et al. Isolation and Characterization of Single Chain Human Antibodies Directed Against Epitopes within Human Platelet GPIba, 1998 ASH abstract, Sept. 1, 1998 (abstract), teaches anti-GPIba-ScFv, HIb-2 which has properties which can make it a candidate for development as a potential and anti-thrombotic agent.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

April 24, 2007

Maher Haddad

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